REMARKS

Obviousness-type double patenting

Claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 59, 72, 73, 75-77, 91-106 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 37-50 of copending Application No. 10/308,135. Applicant has noted that this is a provisional rejection and will submit a terminal disclaimer should claims 37-50 of the '135 application be allowed.

35 U.S.C. 102(b) (anticipation)

Claim 10 stands rejected under 35 U.S.C. 102(b) as being anticipated by ATCC entries HTB 157, 158, and 160 and ATCC entry CRL-2378, designated MA-104 cells. The Examiner states that the specification does not provide a definition of "immunologically tolerated", as the phrase is used in claim 10, and without a definition of "immunologically tolerated," any cell line that doesn't undergo hyperacute rejection when implanted would fall within the scope of the claim.

Applicant submits that the specification of the present application provides a definition for the phrase "immunologically tolerated" by using the phrase as it was known in the art when the application was filed. Specifically, the specification at page 11, lines 15-18 cites to Gustafson, et al., (1993, Tolerance of sheep-goat chimeras to their component cells. *J Reprod Immunol* **23**, 155-68), which found that sheep-goat chimeras were able to **tolerate** skin grafts from their chimeric siblings and **exhibited immune tolerance to their chimeric siblings as measured by the mixed lymphocyte response (MLR)** (emphasis added). It is well known to one of ordinary skill in the art that a mixed lymphocyte response is not performed under the influence of immunosuppressive drugs. Indeed, the sheep-goat chimeras disclosed in Gustafson are "immunologically tolerant" in the sense that they tolerate the cells of both species without the influence of immunosuppressive drugs. Moreover, the tissues of the chimeras, despite their containing cells of both species, are tolerated by the originating

species. The reason for this tolerance is that the interspecific cells of the chimeric embryo cooperate during development before the immune system has developed and the immune system itself becomes chimeric. Such tolerance is demonstrated, for example, by the sheep-goat interspecific chimeras in Fehilly, et al. (1984, Interspecific chimaerism between sheep and goat. *Nature* **307**, 634-6) and Meinecke-Tillmann et al., (1984, Experimental chimaeras–removal of reproductive barrier between sheep and goat. *Nature* **307**, 637-8), which are not rejected by the single species mother in the absence of immunosuppressive drugs. Similarly, the human/non-human primate chimeric cell line of the present invention, which originates from the embryonic cells of two species, is immunologically tolerated by cells from both species without the influence of immunosuppressive drugs.

Applicant further notes that it is well known in the art that tolerance of foreign cells without the need for immunosuppressants is the commonly accepted criterion to be considered immunologically tolerant. As such, this definition of immunologically tolerant is the definition applied in claim 10 to describe a defining characteristic of the chimeric cell line of the present invention, which is not under the influence of immunosuppressants.

The Examiner also cites to Starzl, et al. (1993, Baboon-to-human liver transplantation. *Lancet* **341**, 65-71; and Lambrigts, et al. (1998, *Transplantation* **66**: 547-61) as evidence of cell lines from different species which are immunologically tolerated by one another. In Starzl et al., baboon cells were tolerated for some period of time after being transplanted into humans. The Examiner states that since baboon cells could be immunologically tolerated by a human species, then a cell from a human would also be immunologically tolerated in a baboon and either species could inherently tolerate both of the cited cell lines for some period of time. The Examiner, however, failed to take into account that the humans in Starzl et al. were only tolerant of the baboon cells while under the influence of immunosuppressive drugs. It is well known in the art that different primates do not typically tolerate one another's cells and tissues without immune suppression and the **usual response is a rejection of the foreign cells**, Bartholomew, et al. (1999, Tolerance in a concordant nonhuman primate model.

Transplantation **68**, 1708-16). Accordingly, there would not be a reasonable expectation that the HTB and CRL cell lines in the cited art to be tolerated by both the human and non-human primate species in the absence of immunosuppressive drugs, and the burden is on Examiner to show that the cited cell lines would exhibit such tolerance, such as by citing art which contradicts the art discussed herein or which shows such lines to be so tolerated. However, because the cited cell lines do not express this limitation, they do not anticipate the cell line of claim 10 in the present invention. Withdrawal of this rejection is requested.

35 U.S.C. 112, first paragraph (written description)

Claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 59, 72, 73, 75-77, 91-106 were rejected under 35 U.S.C. 112, first paragraph for lack of written description.

The claimed invention is directed to a human /non-human primate chimeric embryo. Applicant submits that it has satisfied the written description requirement and has reasonably conveyed to one of ordinary skill in the art that applicant had possession of the claimed invention at the time the application was filed. As stated by the Federal Circuit, "an applicant complies with the written description requirement 'by describing the invention, with all its claimed limitations...,' and by using 'such descriptive means as **words**...that set forth the claimed invention.'" *Lockwood v. Amer. Airlines, Inc.*, 107 F.3d 1565 (Fed. Cir. 1997) (emphasis added). In accordance with *Lockwood*, applicant submits that it has satisfied the written description requirement by using words as its descriptive means. Specifically, Applicant has described the present invention as a "chimeric embryo", using this term in the same manner as it is well known and regularly used in the art. By using the term "chimeric embryo" to describe its invention, Applicant has in fact demonstrated that at the time of filing the present application it had conceived of and possessed a "chimeric embryo," which term is well known in the art to refer to an embryo, at all stages of development, comprised of two genetically distinct types of cells.

The following scientific articles demonstrate the meaning of "chimeric embryo" as it is known and used both in the art and the present specification:

Fehilly, et al. (1984) describes the production of sheep-goat chimaeras made by combining sheep embryonic cells with goat embryonic cells to create interspecific chimeric embryos. More specifically, Fehilly demonstrates that blastomeres from a sheep embryo and blastomeres from a goat embryo can be combined to form viable interspecific composite blastocyst that give rise to sheep-goat chimeric embryos and eventually sheep-goat chimeras. Thus, the term chimeric embryo as used in the art and the present specification refers to an embryo, at all stages of development, made from the embryonic cells of two different species or two genetically distinct cells, which likely develops to form a chimeric animal.

Similarly, Meinecke-Tillmann et al. (1984, Experimental chimaeras–removal of reproductive barrier between sheep and goat. *Nature* **307**, 637-8) also describes the production of interspecific chimeric embryos by combining blastomeres from a 4 or 8-cell stage sheep embryo with blastomeres from an 8-cell stage goat embryo. The resulting chimeric embryos were then developed to term and produced sheep-goat and goat-sheep chimeras, i.e. animals which originated from an embryo made up of cells from two different species. Thus, chimeric embryo refers to an embryo, at all stages of development, made from the cells of two distinct species.

Furthermore, Rossant et al., (1983, Somatic and germline mosaicism in interspecific chimaeras between Mus musculus and Mus caroli. *J Embryol Exp Morphol* **73**, 193-205), also reports the successful production of interspecific chimeras from chimeric embryos and analysis of those chimeras revealed that cells of the two different species could coexist and interact normally in all tissues studied.

Therefore, the above articles demonstrate that the term "chimeric embryo," as used in art at the time the application was filed, refers to an embryo made of cells derived from two genetically distinct cells or two different species. This term is used to describe a very broad range of embryonic developmental stages, beginning with the earliest 2, 4, or 8 cell stage of the chimeric embryo and

through its further development until it eventually becomes a multicellular chimeric animal. Similarly, Applicant has described its invention as an embryo made up of two different species, in this case, **a human** and **a non-human primate** (spec., pg. 16, line 13-15) and it has done so by using the term "chimeric embryo," as such term is used in the art (See, Fehilly, et al. (1984) and Meinecke-Tillmann, et al. (1984)). Applicant has set forth the detailed structure of its claimed invention, and has demonstrated possession of a chimeric embryo by providing a clear depiction in the form of words. By using the term "chimeric embryo," as it is defined in the art, Applicant has demonstrated possession of an embryo made from two different species, through all of its developmental stages until it becomes a chimeric animal . As such, conception has occurred and reduction to practice has occurred by the filing of the present application. Accordingly, it is submitted that the specification provides an adequate written description of the claimed invention. Withdrawal of this rejection is requested.

35 U.S.C. 112, first paragraph (enablement)

Claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 50, 53, 55, 59, 72, 73, 75-77, 91-106 were rejected under 35 U.S.C. 112, first paragraph for lack of enablement. Applicant maintains that the technology for producing interspecific chimeric embryos was robust, and the art at the time of filing was replete with techniques for making and using such chimeric embryos. Applicant asserts that the art at the time of filing the present application and the present specification provides the requisite guidance for producing the interspecific chimeric embryos of the present invention without undue experimentation.

The Examiner contends that at the time of filing, the art and the specification did not teach how to produce and culture human/non human primate chimeric embryos. However, as evidenced by the cited references set out below, the methods used to create interspecific chimeric embryos would have been well known to one of ordinary skill in the art and armed with this background it would not have required undue experimentation to create human/non-human chimeric embryos.

For example, Fehilly, et al. (1984), cited in the specification on pages 2-3, reports the successful production of interspecific sheep-goat chimeras by embryo manipulation using three different techniques. First, interspecific chimeric embryos were formed using single blastomeres from 4-cell goat embryos and combining them with single blastomeres from 4-cell sheep embryos or with single blastomeres from 8-cell sheep embryos in evacuated zonae pellucidae. In a second technique, interspecific embryos were produced either by surrounding an 8-cell goat embryo from which the zona pellucida had been removed with blastomeres of three 8-cell sheep embryos or by surrounding an 8-cell sheep embryo with the blastomeres of three 8-cell goat embryos. Finally, a third technique was used to produce interspecific chimeric embryos where the inner cell mass and the polar trophectoderm from day 8 goat blastocyst were inserted into day 8 sheep blastocyst by the technique described in (Gardner, et al. *Nature* **220**, 596-597*)* and in the same way, sheep inner cell masses were combined with goat blastocyst. The interspecific chimeric embryos were cultured and those which developed into normally organized chimeric blastocyst were transferred to recipient ewes or goats. These techniques were implemented successfully to create viable sheep-goat interspecific chimeras.

Meanwhile, Meinecke-Tillmann et al. (1984), also cited in the specification, pg.3, reports the successful production of interspecific goat-lamb chimeras. To produce interspecific chimeric embryos, Meinecke et al. combined one sheep blastomere from a 4-cell stage embryo with two goat blastomeres from an 8-cell stage embryo or two sheep blastomeres from the 'early' 8-cell stage with two goat blastomeres of the 'late' 8-cell stage in a common pig zona pellucida. These chimeric embryos developed to the blastocyst stage and were then transferred to a sheep recipient and brought to term to create sheep-lamb and goat-lamb interspecific chimeras. Additionally, Rossant et al. (1983) also reports the successful production of interspecific chimeras and analysis of those chimeras revealed that cells of the two species could coexist and interact normally in all tissues studied. In Rossant et al. no selection occurred against the cells foreign to the carrier during gestation of the chimaeras.

The art at the time of filing was replete with techniques not only for making interspecific chimeric embryos, but also for culturing interspecific chimeric embryos, and these techniques could be applied in creating human/non-human primate chimeric embryos without undue experimentation. Specifically, Fehilly, et al. (1984) and Meinecke-Tillmann, et al. (1984) describe methods for making interspecific sheep-goat chimeric embryos, and in both studies no special embryo handling techniques beyond those generically used for the handling and cultivation of mammalian embryos were needed. These generic mammalian embryo culturing techniques, which were implemented for the successful culturing of interspecific chimeric embryos in the art cited above, were well known in the art as exemplified by the following references: Pope, C.E. et al. (1982). Development of baboon preimplantation embryos to post-implantation stages *in vitro*. *Biol Reprod* **27**, 915-23; Gould, K. G. (1983). Ovum recovery and in vitro fertilization in the chimpanzee. *Fertil Steril* **40,** 378-83; Pope, V.Z. et al. (1984). SP-I secretion by baboon embryos *in vitro*. *Placenta* **5**, 403-12; Fourie, F.R. et al. (1987). Supplementation of Ham's F10 culture medium with three different sera in the culturing of baboon oocytes. *Comp Biochem Physiol A* **87,** 1103-6; and, Pope, C.E. et al. (1997). Birth of a western lowland gorilla (Gorilla gorilla gorilla) following *in vitro* fertilization and embryo transfer. *Am J Primatol* **41**, 247-60 all report the culture of primate embryos. Moreover,
Machaty et al. (US 6,211,429) and Yanagimachi (US 6,376,743) claim methods of obtaining or producing mammalian embryos, respectively and the disclosures, and references cited therein, enable one of ordinary skill in the art to culture primate embryos, e.g., Homa, S.T., et al. (1994). *Hum Reprod* **9**, 2356-2361 and Herbert, M. (1995). *Hum Reprod* **10**, 2183-2186.

Applicant maintains that the art at the time of filing the present application provided sufficient guidance for producing and culturing interspecific chimeric embryos using aggregation and injection techniques, and was thus, enabling for the production of human/non-human primate interspecific chimeras. Armed with the background provided by the work cited above, it is submitted that undue experimentation would not be required to practice the embodiments of the claimed invention pertaining to the production of chimeras from human embryonic and non-human embryonic cells.

Applicant further submits that the specification is also enabling for the making and use of human and non-human primate embryonic stem (ES) cells to create chimeric embryos. Methods for isolating and culturing human and non-human primate stem cells and using them to make interspecific chimeric embryos were known in the art, and the present invention was created shortly after such methods originated. Thus, the same technology could be used to produce interspecific chimeric human/non-human primate embryos without undue experimentation.

First, Thomson et al. (1995, *Proc Nat Acad Sci USA* **78**, 7634-7638), cited on pg. 4 of the specification, describes the isolation of an ES cell line from the embryo of the rhesus monkey. Thomson suggested that the use of human ES cells would offer "exciting new possibilities for transplantation medicine."

With regard to the generation of human ES cells, although not widely published at the time the application was filed, many groups were using the techniques employed for other mammals to develop human ES cell lines. During the year following filing of the present application, two groups published the isolation of such cell lines (Thomson, J.A. et al. (1998) Embryonic Stem Cell Lines Derived from Human Blastocysts. *Science* **282,** 1145-7; and Shamblott, M.J. et al. (1998). Derivation of Pluripotent Stem Cells from Cultured Human Primordial Germ Cells. *Proc Natl Acad Sci USA* **95,** 13726-31). These ES cell lines were isolated using existing techniques, without "undue experimentation." For example, in reporting the first primate ES cells, Thomson et al. stated: "The growth of monkey ES cells in culture conditions that support feeder-dependent human EC [embryonal carcinoma] cells **suggests that similar conditions may support human ES cells**," (Thomson et al. (1995) at p. 7848; emphasis added). That this understanding was correct was confirmed in the report by this group of the isolation of human ES cells, where it is stated: "five [human] ES cell lines originating from five separate embryos were derived, **essentially as described for nonhuman primate ES cells**," (Thomson et al. (1998) at p. 1145; emphasis added).

Prior to the time of filing, at least one report appeared in the literature of an ES-like cell line derived from human embryos (Bongso, A. et al. (1994). Isolation and culture of inner cell mass cells

from human blastocysts. *Hum Reprod* **9,** 2110-7). This report was referred to by Moreadith and Radford (1997. Gene targeting in embryonic stem cells: the new physiology and metabolism. *J Mol Med* **75**, 208-216) in the following fashion:

> The advent of techniques to generate gain-of-function and loss-of-function mutations in laboratory animals represents one of the major accomplishments in cell and molecular biology in mammals over the past two decades. Although the technology is generally limited only to the mouse at present, substantial effort is underway to develop these techniques, and to refine existing techniques, in other species. Putative pluripotential ES cell lines have been derived in a number of other species including hamster [70], pig [71–75], sheep [73], cattle [76], rabbit [77], rat [78], mink [79], monkey [80], and even humans [81]. Thus it seems likely the technology will be advanced into these additional species over the next few years, and each one of these may lend itself uniquely to problems ranging from development to tissue and organ physiology.

Reference [81] is Bongso et al. (1994). Moreover, it was generally known in the developmental biology community as of late 1997 that the Thomson group at the University of Wisconsin was working towards the isolation of human ES cells (their paper reporting this was published in 1998, and their 1995 paper reporting a primate stem cell line stated: "The growth of monkey ES cells in culture conditions that support feeder-dependent human EC [embryonal carcinoma] cells **suggests that similar conditions may support human ES cells**" (Thomson, 1995, p. 7848; emphasis added). Taken together, these reports and the discussion of Bosgso et al. (1994) by Moreadith and Radford (1997) indicates that by late 1997 knowledge of human ES cells was available to researchers.

Bradley et al. (1984, *Nature* **309**, 255-256), cited on pg. 4 of the specification, discloses techniques that can be used to make interspecific chimeric embryos as claimed in the present invention. More specifically, Bradley et al. teaches that ES cells can be combined with normal pre-implantation embryos of the same or different species from which they are derived and they will participate in the normal development of the embryo and eventually contribute cells to the tissues of the resulting animal.

Further, Nagy et al. (1993, *Proc Nat Acad Sci* **90**, 8424-8428), cited on pg. 5 of the specification, describes an additional technique that can be used for generating chimeric embryos. This article teaches the use of "early passage" ES cells to produce viable mice which are completely ES-cell derived. Specifically, the ES cells are aggregated with defective embryos genetically incapable of advancing beyond the early stages of development, but which provide components that mediate implantation of the chimeric cell aggregates. This technique is based on the aggregation of ES cells with developmentally compromised tetraploid embryos where the ES cells differentiate normally to form viable embryos.

Finally, Goldstein, et al. (2002, Integration and differentiation of human embryonic stem cells transplanted to the chick embryo. *Dev Dyn* **225**, 80-6) discloses that human embryo ES cells were successfully implanted into early stage chicken embryos using stem cell isolation and culturing techniques in existence when the present application was filed. As evidenced by the above cited references, methods of making and using ES cells to create interspecific chimeric embryos would have been well known to one of ordinary skill in the art, and armed with this background it would not have required undue experimentation to create human/non-human chimeric embryos, which were created shortly after techniques had been implemented for making human stem cells and creating chimeric embryos using stem cells. A reasonable expectation of success is evidenced by Goldstein et al. which demonstrates the production of a chimeric embryo of human embryonic cells and embryonic cells from a species more divergent than a non-human primate.

The Examiner states that there is no evidence that a chimeric human/nonhuman primate embryo could be produced by the insertion of a nonhuman primate ES cell into a human embryo, or by the insertion of a human ES cell into a nonhuman primate embryo. The Examiner cites to a quote by J. Rossant in (DeWitt, *Nature* **420**: 255, (2002) col. 2-3, bridg. sent.), which noted that the differences in gestation periods between mice and humans would make it unlikely that the cells would combine in the embryo, and one of skill in the art would have reason to question the ability to make a mouse/human chimeric embryo in light of these differences. From this, the Examiner deduced that

one of skill in the art would have reason to question the ability to make human/non-human primate chimeric embryos without undue experimentation

Applicant submits that the Examiner's concerns regarding the differences between non-human primates and humans, and the ability for a human or non-human primate to survive and be supported during pregnancy, do not hold up in light of Goldstein et al.. That is, Goldstein et al. successfully implanted human embryo stem cells into chicken embryos where they thrived and became incorporated into several organs. Chicken embryos, from a nonmammalian species, are considerably more different from human embryos in biology and developmental rate than are non-human primate embryos. As such, it follows that the proposed human/non-human primate chimeric embryos would also thrive and develop while incorporating both human and non-human primate cells into all of the organs of the resulting chimeric animal. Applicant submits that the specification is enabling for the use of human and non-human primate embryonic stem (ES) cells and maintains that undue experimentation would not have been required to produce the claimed interspecific chimeric embryo through all of its embryonic stages in view of the teachings and knowledge in the art.

The Fehilly, et al. (1984) and Meinecke, et al. (1984) studies cited above also provide further support that interspecific chimeric embryos can be produced and carried to term. In both of those studies the sheep-goat chimeric embryo was implanted in the host female and carried to term to produce a viable sheep-goat chimera. Thus, the techniques known in the art were sufficient to enable and guide an ordinary artisan to implement the claimed invention and create an interspecific human/non-human primate chimeric embryo without undue experimentation.

Applicant maintains that the specification enables not only how to make the human/non-human chimeric embryos but also how to use them. Applicant asserts that it has identified at least one credible utility in the specification by describing how the present invention can be used for performing toxicology assays. The specification specifically states that, this system would be of great utility to pharmaceutical companies and chemical manufacturers who wish to determine the teratogenicity and developmental toxicity of various chemicals. The developing embryos can be

exposed to test drugs or chemical compounds via the tissue culture medium or the maternal circulation, and effects on developmental outcome can be assessed morphologically and histologically. (Specification pg. 19, lines 16-21).

The methodology for using mammalian embryos for toxicology studies was well known in the art at the time the application was filed as indicated by Naruse et al. (1997, Surgical manipulation of mammalian embryos in vitro. *Int J Dev Biol* **41**, 195-8) and Prati et al. (1993, Alternatives to in vivo tests for teratologic screening. *Ann Ist Super Sanita* **29**, 41-6). Armed with the background provided by this work, it is submitted that undue experimentation would not be required to perform toxicology studies using human/non-human chimeric embryos.

In view of the above remarks, it is submitted that the specification fully enables the chimeric embryos as set forth in the claims. Withdrawl of this rejection is requested.

35 U.S.C. 101 (non-statutory subject matter)

Claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 59, 72, 73, 75-77, 91-106 were rejected under 35 U.S.C. 101 as being directed to non-statutory subject matter. Applicant maintains that the rejection is improper for two reasons: (1) the claimed subject matter is not directed to a human being or a human embryo but rather a man-made chimeric embryo and cell lines derived therefrom and (2) even if examiner interprets the claims of the present application to cover human beings, such subject matter would not be unpatentable since the statute does not restrict patentability based upon whether claims embrace a human being.

Regarding the first point, Examiner maintains that the broadest reasonable interpretation of the claims in the present invention includes both human and non-human embryos. Applicant, however, respectfully disagrees because the present claims are directed to a chimeric embryo comprising embryonic cells from a human and a non-human primate wherein said cells **remain attached to one another and cooperate in the formation of a further developing embryo**. The specification specifically states that the invention comprises cells from human embryos and non-

human primate embryos, which have been **aggregated under conditions in which a viable embryo forms**. (Specification, page 16, lines 1-4, emphasis added). The viable embryo that forms is an interspecific chimeric embryo which is neither human or non-human primate, but a distinct embryo made up of two genetically distinct types of cells. See Fehilly, et al. (1984) and Meinecke-Tillmann, et al. (1984) above where sheep cells and goat cells were combined to create a sheep-goat chimera, not a sheep or a goat, but a sheep-goat, which is an organism distinct from either species alone, in recognition of which the name "geep" was coined by the Fehilly group.

Examiner supports her position that the present invention encompasses a human being by stating that a human being may comprise a proportion of non-human cells and still remain a human (citing Starzl et al. (1993)). Starzl reported on the treatment of patients with cells transplanted from a non-human primate (baboon). Examiner stated that in Starzl, et al. the addition of a proportion of baboon cells to the human did not convert the human patient to a non-human, and thus, applicant's general argument that embryos not exclusively human **in origin** are not human is unpersuasive. However, the present invention can be distinguished from Starzl, et al., and the chimeric humans it discloses, because the human/non-human primate chimeric embryo of the present invention was never exclusively human in origin since it originated as a combination of cells from two different species. The chimeric embryo of the present invention, which develops into a chimeric animal, was never solely a human embryo or a non-human primate embryo, but instead, was a combination of two distinct species from the beginning of its existence.

In contrast, the human being in Starzl, et al. was a fully developed human being originating solely from a human embryo. The human being in Starzl, et al. was exclusively human in origin, and as such, the transplanting of cells to a human being would not convert the human into a non-human and change its origin. In distinction, the chimeric embryo of the present invention was never exclusively human in origin. The chimeric embryo never existed as a human embryo or a non-human embryo. That is, it the chimeric embryo did not exist until human embryonic and non-human embryonic cells were combined to create the chimeric embryo. Moreover, because of the early

embryonic stages employed to create the chimeric embryo, in accordance with techniques known in the art at the time of filing, the resulting interspecific chimeric animal contains cell contributions from both species throughout all of its organs, unlike the human in Starzl, et al., which only had a single baboon organ transplanted to it, the cells of which disseminated into human tissues by an **entirely different route and mechanism** than that of interspecific embryo chimeras. Correspondingly, the final nonhuman to human DNA ratio in the patient described was 1:1,000 to 1:10,000, rather than the 100:1 to 1:100 (depending on the technique used) characteristic of interspecific mammalian embryo chimeras. Because the cells in interspecific chimeras are mixed before they have differentiated, the chimera's tissues ultimately contain organ-specific cells of both originating species, which is not the case in Starzl et al., where the nonhuman cells in the human tissues appear to have been mainly blood, according to the investigators. Thus, the chimeric embryo of the present invention was never exclusively human and its broadest interpretation, whether it consists of 100 human cells and one non-human cell or vice-versa, could never encompass a human embryo or human being like the type disclosed in Starzl, et al.

Further supporting applicants position that the chimeric embryos claimed in the present invention are not human beings is the Supreme Court's decision in *Roe v. Wade*, 410 U.S. 113 (1973). The Supreme court has held that embryos, even those consisting exclusively of human cells, are not constitutionally protected as human beings. *Id.* Congress – in spite of almost 30 years of vigorous public debate – has indicated no intention of altering this holding. That holding is mandatory authority and precludes the examiner's finding that a single cell is sufficient to make a human being.

As to the second point, Applicant further maintains that the statute does not restrict patentability based upon whether claims embrace a human being. Nowhere does the statute restrict patentability based upon embracing a human being. The Examiner recognizes that the Court in *Chakrabarty* (*Diamond v. Chakrabarty,* 447 U.S. 303 (1980)) held that statutory subject matter shall "include anything under the sun that is made by man." (at 309). The claimed subject matter is not naturally occurring. It is not disputed by the Examiner that the claimed subject matter is "made by

man." Applicant claims a chimeric embryo or a cell line derived from the chimeric embryo. A human being is not claimed.

The Federal Circuit recently emphasized in *State Street Bank* (*State Street Bank & Trust Co. v. Signature Financial Group,* 149 F.3d 1368 (Fed. Cir. 1998)) that neither courts nor the Patent Office are authorized to embellish the statutory requirements for patentability. The Federal Circuit confronted the so-called "mathematical algorithm" and "business method" exceptions to patentability (at 1373, 1375-76):

> The repetitive use of the expansive term "any" in § 101 shows Congress's intent not to place any restrictions on the subject matter for which a patent may be obtained beyond those specifically recited in § 101. Indeed, the Supreme Court has acknowledged that Congress intended § 101 to extend to "anything under the sun that is made by man." *Diamond v. Chakrabarty,* 447 U.S. 303, 309, 100 S.Ct. 2204, 65 L.Ed.2d 144 (1980); *see also Diamond v. Diehr,* 450 U.S. 175, 182, 101 S.Ct. 1048, 67 L.Ed.2d 155 (1981).[3] Thus, it is improper to read limitations into § 101 on the subject matter that may be patented where the legislative history indicates that Congress clearly did not intend such limitations. *See Chakrabarty,* 447 U.S. at 308, 100 S.Ct. 2204 ("We have also cautioned that courts 'should not read into the patent laws limitations and conditions which the legislature has not expressed.' " (citations omitted)).
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> [3] The Committee Reports accompanying the 1952 Act inform us that Congress intended statutory subject matter to "include anything under the sun that is made by man." S. Rep. No. 82-1979 at 5 (1952); H.R. Rep. No. 82-1923 at 6 (1952).

As the "embraces a human being" exception grafted by the Examiner in this case, these exceptions enjoyed no statutory sanction. Unlike the "embraces a human being" exception, they enjoyed prior judicial and Patent Office application in varying degrees.

As the Federal Circuit has held so clearly in *State Street,* "any" invention "made by man" is patentable subject matter. It is for Congress -- not the courts or the Patent Office -- to set forth any limitations on patentable subject matter. Congress has not established any limitation based on subject matter that "embraces a human being." The Commissioner lacks the authority to impose one under Section 101. Whether or not the Patent Office believes Congress intended to bar patentability of

inventions that embrace a human being is not the issue. Congress has not done so expressly and the Patent Office has no authority to fill that gap.

In view of the above remarks, it is submitted that the rejection of the claims for lack of patentable subject matter is improper. Withdrawal of this rejection is requested.

35 U.S.C. 101 (patentable utility)

1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 59, 72, 73, 75-77, 91-106 were rejected under 35 U.S.C. 101 as lacking patentable utility. The Examiner is aware that applicant can satisfy the requirement of showing the claimed invention has a patentable utility by showing that the invention has one credible utility. Further, this utility does not even need to be disclosed in the application, if it is known by a skilled artisan. Nevertheless, Applicant maintains that it has identified a credible utility in the specification, that is, the present invention will be useful for performing toxicology and teratology studies. The specification specifically states that this system would be of great utility to pharmaceutical companies and chemical manufacturers who wish to determine the teratogenicity and developmental toxicity of various chemicals. The developing embryos can be exposed to test drugs or chemical compounds via the tissue culture medium or the maternal circulation, and effects on developmental outcome can be assessed morphologically and histologically. (Specification, pg. 19, lines 16-21). Contrary to the Examiner's belief, use of the chimeric embryos claimed in the present invention for toxicology and teratology studies is not general or meaningless, but it is a specific credible utility as exemplified in the following scientific articles which show that whole embryo culture of mammalian embryos is increasingly being used for such studies.

For example, Naruse et al. (1997), states that "whole-embryo culture systems are useful in the fields of not only embryology but also teratology, toxicology, pharmacology, and physiology." Whole embryo culture allows for surgical manipulation of mammalian embryos which alters the destiny of morphogenesis of the embryos and helps answer questions concerning developmental issues. Also, Prati et al. (1993), indicates that rodent whole embryo cultures for both pre- and post-implantation

embryos are useful in the screening of teratogens. Both articles provide the methodology for performing toxicology or teratology studies on mammalian embryos, techniques that were well known in the art at the time the present application was filed.

In a similar fashion, the chimeric embryos of the present invention can be used for performing toxicological and teratological testing. Such testing can be used to assess cellular damage or aberrant responses in terms of gene expression in embryonic cells. Because it is unethical to use human embryos for such toxicological and teratological testing, this invention provides the next best alternative in the form of a chimeric embryo which has non-human status since it is composed of both human and non-human primate components. Toxicology and teratology studies performed on human/non-human primate chimeric embryos are specific credible utilities as indicated by the references cited above and will provide real and commercial benefits.

Copies of the newly cited references are attached.

In view of the above remarks, it is submitted that the claimed chimeric embryos have at least one specific, credible utility. Withdrawal of this rejection is requested.

In view of the above remarks, it is believed that the present claims satisfy the provisions of the patent statutes and are patentable over the cited prior art. Reconsideration of the application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned to expedite the prosecution of the application.

Respectfully submitted,

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By _____

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Attachments:

Fehilly, C.B. et al. (1984). "Interspecific Chimaerism Between Sheep and Goat," *Nature* **307**:634-636.

Bartholomew, A.M. et al. (1999). "Tolerance in a Concordant Nonhuman Primate Model," *Transplantation* **68**:1708-1716.

Goldstein, R.S. et al. (2002). "Integration and Differentiation of Human Embryonic Stem Cells Transplanted to the Chick Embryo," *Devel. Dynamics* **225**:80-86.

Gustafson, R.A. et al. (1993). "Tolerance of Sheep-Goat Chimeras to Their Component Cells," *J. Reprod. Immunol.* **23**:155-168.

Naruse, I. et al. (1997). "Surgical Manipulation of Mammalian Embryos *in Vitro*," *Int. J. Dev. Biol.* **41**:195-198.

Prather, R.S. et al. (1989). "Preimplantation Mammalian Aggregation and Injection Chimeras," *Gamete Res.* **22**:233-247.

Rossant, J. et al. (1983). "Somatic and Germline Mosaicism in Interspecific Chimaeras between *Mus musculus* and *Mus caroli,*" *J. Embryol. Exp. Morphol.* **73**:193-205.

Starzl, T.E. et al. (1993). "Baboon-to-Human Liver Transplantation," *Lancet* **341**:65-71.